Division of Intramural Research

NAEHS Council Update

February 2015

DIR RECRUITMENTS

Investigators in Epidemiology
The National Institute of Environmental Health Sciences is recruiting for one or more full-time Tenure-Track Epidemiologists. The successful candidate(s) will be expected to develop an outstanding, investigator-initiated independent epidemiology research program on human health outcomes. Applicants are welcome with expertise in any of the following areas: reproduction, pregnancy outcomes, pediatric outcomes, early origins of disease, life course epidemiology, adult health/chronic disease, or other areas of environmental epidemiology. Biologically-based epidemiological research (including genetics, epigenetics, metabolomics, microbiomics, and biomarkers) is especially encouraged. Successful candidates will be expected to have the ability to work independently and as part of multi-disciplinary and/or collaborative teams. Candidates should have a Doctoral degree and a record of accomplishment in epidemiology, including a strong publication record and research experience. Dr. Janet Hall, NIEHS Clinical Director, is chair of the search committee.

Deputy Chief of the Comparative Medicine Branch
The National Institute of Environmental Health Sciences (NIEHS) is searching for Veterinary Medical Officer to serve as Deputy Chief of the Comparative Medicine Branch (CMB), Facility Veterinarian, and Deputy Animal Program Director. CMB provides a broad range of services and collaborative support for NIEHS intramural research programs. The incumbent will be responsible for assisting the Chief CMB with the management of an AAALAC accredited animal care and use program and for support of NIEHS animal research programs that study the effects of environmental agents in order to develop methods of disease prevention and treatment. Candidates should have a Doctor of Veterinary Medicine (DVM) or equivalent degree, i.e., Veterinary Medical Doctor (VMD), obtained at a school or college of veterinary medicine accredited by the American Veterinary Medical Association Council on Education; have a permanent, full, and unrestricted license to practice veterinary medicine in a State, District of Columbia, the Commonwealth of Puerto Rico, or a territory of the United States; and be board certified by the American College of Laboratory Animal Medicine (ACLAM) or equivalent. Dr. Kathy Laber, Chief of the Comparative Medicine Branch, is chair of the search committee.

Scientific Information Officer
The National Institute of Environmental Health Sciences is searching for an exceptional candidate to serve as the Scientific Information Officer (SIO). The SIO will head a dynamic office focused on the interface between cutting edge scientific computing and scientific exploration, discovery and translation. It is critical that our institute is able to fully harness advances in scientific computing and science information technology to meet our research mission. We are seeking an outstanding leader who will create an environment where scientific computing catalyzes our research program. The successful candidate will: 1). Advise the NIEHS Scientific Director, Division of the National Toxicology Program Director, NIEHS Leadership and other experts throughout the NIEHS on a variety of complex, unique and/or sensitive situations and issues in scientific computing; 2). Provide a vision for scientific computing and the extraction and use of knowledge from the data generated by and relevant to NIEHS research; 3). Lead the NIEHS in application of new methods and technologies emerging from the field of data science and "big data" as well as advancing the use of cloud and distributed computing

approaches; 4). Coordinate ongoing scientific computing activities with other Institutes/Centers throughout NIH, other federal agencies and other institutions as it relates to fostering the adoption and training of new, effective technologies and procedures for scientific computing and manipulating and interpreting large and complex data generated by researchers in the environmental health sciences community; 5). Set up relevant training and educational programs to ensure scientists at NIEHS are knowledgeable about the institute resources in these areas; 6). Work in concert with the Chief Information Officer (CIO) at NIEHS to ensure that NIEHS IT assets are planned for and deployed to meet needs; and 7). Work with other NIEHS groups that consume and provide scientific IT capabilities including the Integrated Bioinformatics Core Facility and Biostatistics/Computational Biology Branch to ensure effective use of NIEHS resources. Applicants should have a degree in a biological science, agriculture, natural resource management, chemistry, or related disciplines appropriate to this position. Dr. Trevor Archer, Chief, Epigenetics and Stem Cell Biology Laboratory, is chair of the search committee.

NEW HIRES AND CHANGES IN DIR LEADERSHIP

Clinical Director
Dr. Janet Hall has accepted our offer to be Clinical Director at NIEHS. Dr. Hall was a Professor of Medicine at Harvard University and served as Associate Chief of the Reproductive Endocrine Unit at Massachusetts General Hospital. Dr. Hall received her M.D. in 1981 from McMaster University, completed her residency in Internal Medicine at McMaster University and an Endocrinology fellowship at Massachusetts General Hospital. She is an international recognized physician-scientist who studies human reproductive physiology and pathophysiology with a view to translating this information to benefit women with reproductive disorders. She is the Past-President of the Endocrine Society which has over 17,000 members worldwide. She also has served on numerous NIH Special Emphasis Panels and numerous Editorial Boards. Dr. Hall began to begin work at NIEHS on September 21, 2014.

Earl Stadtman Tenure-Track Investigators
Dr. Robin Stanley from the Laboratory of Molecular Biology at National Institute of Diabetes and Digestive and Kidney Diseases, NIH, Bethesda, MD, has been offered a tenure-track position in DIR at NIEHS. Dr. Stanley studies the regulation of autophagy and ribosome biogenesis by the target of rapamycin (TOR) signal transduction pathway. Dr. Stanley has accepted our offer and will have a primary appointment in the Signal Transduction Laboratory and a secondary appointment in the Genomic Integrity and Structural Biology Laboratory. Dr. Stanley started at NIEHS July 28, 2014.

Biostatistics, Bioinformatics, and Computational Biology
Dr. Shanshan Zhao from the Fred Hutchinson Cancer Research Center, Seattle, WA, has been offered a tenure-track position in DIR at NIEHS. Dr. Zhao has statistical interests in mediation analysis, error, and high dimensional data. Dr. Zhao has accepted our provisional tenure-track offer. She will have a primary appointment in the Biostatics and Computational Biology Branch and a secondary appointment in the Epidemiology Branch. Dr. Zhao started at NIEHS on January 12, 2015.

Molecular and Cellular Signaling, Neuroscience, and Developmental or Reproductive Biology
Dr. Dante Bortone from the Center for Neural Circuits and Behavior, Howard Hughes Medical Institute, University of California-San Diego, La Jolla, CA, has been offered a tenure-track position in DIR at NIEHS. Dr. Bortone studies the developmental origin of neurons in the visual cortex. Dr. Bortone has accepted our provisional tenure-track offer. He will have a primary appointment in the Neurobiology Laboratory and a secondary appointment in the Reproductive and Developmental Biology Laboratory. His tentative start date is in the spring 2015.

Dr. Guohong Cui from the Laboratory of Integrative Neuroscience, National Institute on Alcohol Abuse and Alcoholism, NIH, Rockville, MD, has been offered a tenure-track position in DIR at NIEHS. Dr. Cui studies the development and function of brain circuits involved in reward processing and locomotion. Dr. Cui has accepted our tenure-track offer. He will have a primary position in the Neurobiology Laboratory and a secondary appointment in the Reproductive and Developmental Biology Laboratory. He started at NIEHS October 24, 2014.

Dr. Jennifer Martinez from the Department of Immunology, St. Jude Children's Research Hospital, Memphis, TN, has been offered a tenure-track position in DIR at NIEHS. Dr. Martinez studies how cells of the innate immune system process extracellular material, and how these events affect subsequent immune responses. Dr. Martinez has accepted our provisional tenure-track offer. She will have a primary appointment in the Immunity, Inflammation and Disease Laboratory and a secondary appointment in the Signal Transduction Laboratory. Her tentative start date is March 1, 2015.

Dr. Francesco DeMayo from the Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX, has tentatively accepted a position as a tenured Senior Scientist in the Reproductive and Developmental Biology Laboratory. Dr. DeMayo investigates the molecular regulation of cellular differentiation and physiology in the lung and uterus in order to shed light on molecular pathways to aid in the diagnosis and treatment of human disease with the goal of helping the design treatments for pulmonary diseases and infertility. He is scheduled to start at NIEHS in the summer of 2015.

Lasker Clinical Research Scholar

Dr. Natalie Shaw from the Department of Pediatrics, Harvard Medical School, Boston MA, has tentatively accepted a position as a NIH Lasker Clinical Research Scholar in DIR at NIEHS. She will have a primary appointment in the Clinical Research Branch and a secondary appointment in the Reproductive and Developmental Biology Laboratory. Dr. Shaw investigates the environmental and hormonal factors that control puberty. Using clinical research tools she explores how the sleep centers of the brain may influence the hypothalamic gonadotropin-releasing hormone (GnRH) neuronal network that drives the reproductive axis. She is scheduled to start at NIEHS in the Fall of 2015.

DIR RESEARCH UPDATE

Epidemiology:

Contributing to basic science by looking at the big picture

Allen Wilcox, M.D., Ph.D.

Epidemiology Branch, DIR NIEHS

Epidemiology is usually thought of as the scientific arm of public health. The macro-level observations of epidemiology can also provide insights or raise fundamental hypotheses of interest to laboratory scientists. Some examples come from NIEHS epidemiologic studies of fertility and pregnancy. The number of fertile days in a typical human menstrual cycle – long underestimated by biologists – was resolved in an epidemiologic study. Another example from epidemiology is the discovery of a connection between the rate of development of a fertilized human egg and the rate of fetal maturation. Finally, new data show a connection between a mother's age and gene methylation in her newborn – suggesting the possibility of undiscovered mechanisms of methylation.

NIEHS SIGNS AGREEMENT WITH NANJING MEDICAL UNIVERSITY

NIEHS has entered into a partnership with one of the largest universities in China, Nanjing Medical University. As a result of joining forces, the two institutions will exchange scientists and collaborate on environmental health research projects. Darryl Zeldin, M.D., NIEHS Scientific Director, traveled to Nanjing to sign a Memorandum of Understanding. The agreement will permit up to three early-stage university scientists to do research for two to three years at NIEHS, and allow NIEHS senior scientists to lecture at seminars, workshops, school courses, and meetings at the university. The goal is to enhance collaborations and interactions between the two institutions. The partnership would not have been formed without Kenneth S. Korach, Ph.D., Chief Reproductive and Developmental Biology Laboratory. He and Associate Dean of the Nanjing Medical University School of Public Health Yankai Xia, M.D., Ph.D., who are longtime colleagues, were discussing future research plans. When Xia indicated that the university was interested in doing more environmental health studies and establishing core facilities that were similar to the ones at NIEHS, Korach thought it was an opportunity NIEHS couldn't pass up. Air and water pollution are major problems in China, so the School of Public Health is in a unique position to study the impacts on Chinese citizens. Established in 1934, Nanjing Medical University has 17 schools and one independent school, 23 affiliated hospitals, and more than 50 teaching hospitals. The school has an excellent record of grant funding, ranking second only to China's largest educational institution, Peking University Health Science Center. The agreement was signed October 27, 2014.

NIEHS SCIENCE DAYS

The Twelfth Annual NIEHS Science Days were held on November 6-7, 2014, at the Rall Building on the NIEHS Campus to celebrate the achievements of NIEHS scientists. The event was open to the public and more than 250 attendees from universities and research institutions in the Triangle Area attended. NIEHS Science Day consisted of a mini-symposium on Neurobiology in Environmental Health Sciences in which presentations were given by scientists in DIR, DNTP and DERT, a presentation by a former NIEHS trainee, 12 oral presentations given by fellows, students, and technicians, 96 poster presentations and an Awards Ceremony. Judging for the awards was done by Extramural Scientists from universities and research organizations in the Triangle Area, Intramural Scientists and the NIEHS Trainees Assembly.

Mentor of the Year: Samuel H. Wilson, M.D., Genome Integrity & Structural Biology Laboratory
Fellow of the Year: Quaker E. Harmon, M.D., Ph.D., Epidemiology Branch
Best Poster Presentation:

1. Sara N. Andres, Ph.D., Genome Integrity & Structural Biology Laboratory, "Ctp1 tetramers orchestrate DNA end binding and bridging in DNA double strand break repair"
2. Hideki Nakano, Ph.D., Immunity, Inflammation & Disease Laboratory, "Chemokines coordinate differentiation and trafficking of dendritic cells"
3. Katie A. Burns, Ph.D., Reproductive and Developmental Biology Laboratory, Chemoattractants and cytokines play key roles in the early initiation of endometriosis-like disease in an immunocompetent mouse model"
4. Douglas Ganini da Silva, Ph.D., Immunity, Inflammation & Disease Laboratory, "Incorporation of iron to MnSODs leads to the formation of a peroxidase: possible implications for iron toxicity"
5. Hrisavgi D. Kondilis-Mangum, Ph.D., Epigenetics & Stem Cell Biology Laboratory, "DNA methyltransferases play non-redundant roles during B cell maturation and activation"
6. Jennifer A. Bradbury, Immunity, Inflammation & Disease Laboratory, "Soluble Epoxide Hydrolase Regulates Macrophage Phagocytosis and Lung Bacterial Clearance of Streptococcus Pneumoniae"
7. Sophia Harlid, Ph.D., Epigenetics & Stem Cell Biology Laboratory, "Early life exposure to genistein and downstream effects on DNA methylation and gene expression"
8. Matthew J. Schellenberg, Ph.D., Genome Integrity & Structural Biology Laboratory, "Recognition of Poly-Ubiquitin by the DNA-Damage Repair Protein Tdp2"
9. Natacha Steinckwich Besancon, Ph.D., Signal Transduction Laboratory, "Role of the calcium sensor protein, STIM1, in neutrophil chemotaxis and infiltration into psoriatic inflamed skin"

Best Oral Presentation: Georgia M. Alexander, Ph.D., Neurobiology Laboratory, "Manipulating Hippocampal Network Oscillations Critical to Cognition: Implications for Schizophrenia"

DIR PAPERS OF THE YEAR FOR 2014

Henriques T, Gilchrist DA, Nechaev S, Bern M, Muse GW, Burkholder A, Fargo DC, Adelman K. Stable pausing by RNA polymerase II provides an opportunity to target and integrate regulatory signals. *Mol. Cell,* **52:** 517-528, 2013.

> Metazoan gene expression is often regulated after the recruitment of RNA polymerase II (Pol II) to promoters, through the controlled release of promoter-proximally paused Pol II into productive RNA synthesis. Despite the prevalence of paused Pol II, very little is known about the dynamics of these early elongation complexes or the fate of the short transcription start site-associated (tss) RNAs they produce. Here, we demonstrate that paused elongation complexes can be remarkably stable, with half-lives exceeding 15 min at genes with inefficient pause release. Promoter-proximal termination by Pol II is infrequent, and released tssRNAs are targeted for rapid degradation. Further, we provide evidence that the predominant tssRNA species observed are nascent RNAs held within early elongation complexes. We propose that stable pausing of polymerase provides a temporal window of opportunity for recruitment of factors to modulate gene expression and that the nascent tssRNA represents an appealing target for these interactions.

Tumbale P, Williams JS, Schellenberg MJ, Kunkel TA, Williams RS. Aprataxin resolves adenylated RNA-DNA junctions to maintain genome integrity. *Nature,* **506:** 111-115, 2014.

> Faithful maintenance and propagation of eukaryotic genomes is ensured by three-step DNA ligation reactions used by ATP-dependent DNA ligases. Paradoxically, when DNA ligases encounter nicked DNA structures with abnormal DNA termini, DNA ligase catalytic activity can generate and/or exacerbate DNA damage through abortive ligation that produces chemically adducted, toxic 5'-adenylated (5'-AMP) DNA lesions. Aprataxin (APTX) reverses DNA adenylation but the context for deadenylation repair is unclear. Here we examine the importance of APTX to RNase-H2-dependent excision repair (RER) of a lesion that is very frequently introduced into DNA, a ribonucleotide. We show that ligases generate adenylated 5' ends containing a ribose characteristic of RNase H2 incision. APTX efficiently repairs adenylated RNA-DNA, and acting in an RNA-DNA damage response (RDDR), promotes cellular survival and prevents S-phase checkpoint activation in budding yeast undergoing RER. Structure-function studies of human APTX-RNA-DNA-AMP-Zn complexes define a mechanism for detecting and reversing adenylation at RNA-DNA junctions. This involves A-form RNA binding, proper protein folding and conformational changes, all of which are affected by heritable APTX mutations in ataxia with oculomotor apraxia 1. Together, these results indicate that accumulation of adenylated RNA-DNA may contribute to neurological disease.

Li R, Grimm SA, Chrysovergis K, Kosak J, Wang X, Du Y, Burkholder A, Janardhan K, Mav D, Shah R, Eling TE, Wade PA. Obesity, rather than diet, drives epigenomic alterations in colonic epithelium resembling cancer progression. *Cell Metab.,* **19:** 702-711, 2014.

> While obesity represents one of several risk factors for colorectal cancer in humans, the mechanistic underpinnings of this association remain unresolved. Environmental stimuli,

including diet, can alter the epigenetic landscape of DNA cis-regulatory elements affecting gene expression and phenotype. Here, we explored the impact of diet and obesity on gene expression and the enhancer landscape in murine colonic epithelium. Obesity led to the accumulation of histone modifications associated with active enhancers at genomic loci downstream of signaling pathways integral to the initiation and progression of colon cancer. Meanwhile, colon-specific enhancers lost the same histone mark, poising cells for loss of differentiation. These alterations reflect a transcriptional program with many features shared with the program driving colon cancer progression. The interrogation of enhancer alterations by diet in colonic epithelium provides insights into the biology underlying high-fat diet and obesity as risk factors for colon cancer.

Wang L, Du Y, Ward JM, Shimbo T, Lackford B, Zheng X, Miao YL, Zhou B, Han L, Fargo DC, Jothi R, Williams CJ, Wade PA, Hu G. INO80 facilitates pluripotency gene activation in embryonic stem cell self-renewal, reprogramming, and blastocyst development. *Cell Stem Cel*l, **14:** 575-591, 2014.

The master transcription factors play integral roles in the pluripotency transcription circuitry of embryonic stem cells (ESCs). How they selectively activate expression of the pluripotency network while simultaneously repressing genes involved in differentiation is not fully understood. Here, we define a requirement for the INO80 complex, a SWI/SNF family chromatin remodeler, in ESC self-renewal, somatic cell reprogramming, and blastocyst development. We show that Ino80, the chromatin remodeling ATPase, co-occupies pluripotency gene promoters with the master transcription factors, and its occupancy is dependent on OCT4 and WDR5. At the pluripotency genes, Ino80 maintains an open chromatin architecture and licenses recruitment of Mediator and RNA polymerase II for gene activation. Our data reveal an essential role for INO80 in the expression of the pluripotency network and illustrate the coordination among chromatin remodeler, transcription factor, and histone-modifying enzyme in the regulation of the pluripotent state.

Loth DW, Artigas MS, Gharib SA, Wain LV, Franceschini N, Koch B, Pottinger TD, Smith AV, Duan Q, Oldmeadow C, Lee MK, Strachan DP, James AL, Huffman JE, Vitart V, Ramasamy A, Wareham NJ, Kaprio J, Wang XQ, Trochet H, Kähönen M, Flexeder C, Albrecht E, Lopez LM, de Jong K, Thyagarajan B, Alves AC, Enroth S, Omenaas E, Joshi PK, Fall T, Viñuela A, Launer LJ, Loehr LR, Fornage M, Li G, Wilk JB, Tang W, Manichaikul A, Lahousse L, Harris TB, North KE, Rudnicka AR, Hui J, Gu X, Lumley T, Wright AF, Hastie ND, Campbell S, Kumar R, Pin I, Scott RA, Pietiläinen KH, Surakka I, Liu Y, Holliday EG, Schulz H, Heinrich J, Davies G, Vonk JM, Wojczynski M, Pouta A, Johansson A, Wild SH, Ingelsson E, Rivadeneira F, Völzke H, Hysi PG, Eiriksdottir G, Morrison AC, Rotter JI, Gao W, Postma DS, White WB, Rich SS, Hofman A, Aspelund T, Couper D, Smith LJ, Psaty BM, Lohman K, Burchard EG, Uitterlinden AG, Garcia M, Joubert BR, McArdle WL, Musk AB, Hansel N, Heckbert SR, Zgaga L, van Meurs JB, Navarro P, Rudan I, Oh YM, Redline S, Jarvis DL, Zhao JH, Rantanen T, O'Connor GT, Ripatti S, Scott RJ, Karrasch S, Grallert H, Gaddis NC, Starr JM, Wijmenga C, Minster RL, Lederer DJ, Pekkanen J, Gyllensten U, Campbell H, Morris AP, Gläser S, Hammond CJ, Burkart KM, Beilby J, Kritchevsky SB, Gudnason V, Hancock DB, Williams OD, Polasek O, Zemunik T, Kolcic I, Petrini MF, Wjst M, Kim WJ, Porteous DJ, Scotland G, Smith BH, Viljanen A, Heliövaara M, Attia JR, Sayers I, Hampel R, Gieger C, Deary IJ, Boezen HM,

Newman A, Jarvelin MR, Wilson JF, Lind L, Stricker BH, Teumer A, Spector TD, Melén E, Peters MJ, Lange LA, Barr RG, Bracke KR, Verhamme FM, Sung J, Hiemstra PS, Cassano PA, Sood A, Hayward C, Dupuis J, Hall IP, Brusselle GG, Tobin MD, London SJ. Genome-wide association analysis identifies six new loci associated with forced vital capacity. *Nat. Genet.,* **46:** 669-677, 2014.

Forced vital capacity (FVC), a spirometric measure of pulmonary function, reflects lung volume and is used to diagnose and monitor lung diseases. We performed genome-wide association study meta-analysis of FVC in 52,253 individuals from 26 studies and followed up the top associations in 32,917 additional individuals of European ancestry. We found six new regions associated at genome-wide significance ($P < 5 \times 10\text{-}8$) with FVC in or near EFEMP1, BMP6, MIR129-2-HSD17B12, PRDM11, WWOX and KCNJ2. Two loci previously associated with spirometric measures (GSTCD and PTCH1) were related to FVC. Newly implicated regions were followed up in samples from African-American, Korean, Chinese and Hispanic individuals. We detected transcripts for all six newly implicated genes in human lung tissue. The new loci may inform mechanisms involved in lung development and the pathogenesis of restrictive lung disease.

Gale SC, Gao L, Mikacenic C, Coyle SM, Rafaels N, Murray Dudenkov T, Madenspacher JH, Draper DW, Ge W, Aloor JJ, Azzam KM, Lai L, Blackshear PJ, Calvano SE, Barnes KC, Lowry SF, Corbett S, Wurfel MM, Fessler MB. APOε4 is associated with enhanced in vivo innate immune responses in human subjects. *J. Allergy Clin. Immunol.*, **134:** 127-124, 2014.

BACKGROUND: The genetic determinants of the human innate immune response are poorly understood. Apolipoprotein (Apo) E, a lipid-trafficking protein that affects inflammation, has well-described wild-type (ε3) and disease-associated (ε2 and ε4) alleles, but its connection to human innate immunity is undefined.
OBJECTIVE: We sought to define the relationship of APOε4 to the human innate immune response.
METHODS: We evaluated APOε4 in several functional models of the human innate immune response, including intravenous LPS challenge in human subjects, and assessed APOε4 association to organ injury in patients with severe sepsis, a disease driven by dysregulated innate immunity.
RESULTS: Whole blood from healthy APOε3/APOε4 volunteers induced higher cytokine levels on ex vivo stimulation with Toll-like receptor (TLR) 2, TLR4, or TLR5 ligands than blood from APOε3/APOε3 patients, whereas TLR7/8 responses were similar. This was associated with increased lipid rafts in APOε3/APOε4 monocytes. By contrast, APOε3/APOε3 and APOε3/APOε4 serum neutralized LPS equivalently and supported similar LPS responses in Apoe-deficient macrophages, arguing against a differential role for secretory APOE4 protein. After intravenous LPS, APOε3/APOε4 patients had higher hyperthermia and plasma TNF-α levels and earlier plasma IL-6 than APOε3/APOε3 patients. APOE4-targeted replacement mice displayed enhanced hypothermia, plasma cytokines, and hepatic injury and altered splenic lymphocyte apoptosis after systemic LPS compared with APOE3 counterparts. In a cohort of 828 patients with severe sepsis, APOε4 was associated with increased coagulation system failure among European American patients.

CONCLUSIONS: APOε4 is a determinant of the human innate immune response to multiple TLR ligands and associates with altered patterns of organ injury in human sepsis.

Zhang J, Tan D, DeRose EF, Perera L, Dominski Z, Marzluff WF, Tong L, Hall TM. Molecular mechanisms for the regulation of histone mRNA stem-loop-binding protein by phosphorylation. *Proc. Natl. Acad. Sci. USA.*, **111:** E2937-E2946, 2014.

Replication-dependent histone mRNAs end with a conserved stem loop that is recognized by stem-loop-binding protein (SLBP). The minimal RNA-processing domain of SLBP is phosphorylated at an internal threonine, and Drosophila SLBP (dSLBP) also is phosphorylated at four serines in its 18-aa C-terminal tail. We show that phosphorylation of dSLBP increases RNA-binding affinity dramatically, and we use structural and biophysical analyses of dSLBP and a crystal structure of human SLBP phosphorylated on the internal threonine to understand the striking improvement in RNA binding. Together these results suggest that, although the C-terminal tail of dSLBP does not contact the RNA, phosphorylation of the tail promotes SLBP conformations competent for RNA binding and thereby appears to reduce the entropic penalty for the association. Increased negative charge in this C-terminal tail balances positively charged residues, allowing a more compact ensemble of structures in the absence of RNA.

Oldfield AJ, Yang P, Conway AE, Cinghu S, Freudenberg JM, Yellaboina S, Jothi R. Histone-fold domain protein NF-Y promotes chromatin accessibility for cell type-specific master transcription factors. *Mol. Cell,* **55:** 708-722, 2014.

Cell type-specific master transcription factors (TFs) play vital roles in defining cell identity and function. However, the roles ubiquitous factors play in the specification of cell identity remain underappreciated. Here we show that the ubiquitous CCAAT-binding NF-Y complex is required for the maintenance of embryonic stem cell (ESC) identity and is an essential component of the core pluripotency network. Genome-wide studies in ESCs and neurons reveal that NF-Y regulates not only genes with housekeeping functions through cell type-invariant promoter-proximal binding, but also genes required for cell identity by binding to cell type-specific enhancers with master TFs. Mechanistically, NF-Y's distinct DNA-binding mode promotes master/pioneer TF binding at enhancers by facilitating a permissive chromatin conformation. Our studies unearth a conceptually unique function for histone-fold domain (HFD) protein NF-Y in promoting chromatin accessibility and suggest that other HFD proteins with analogous structural and DNA-binding properties may function in similar ways.

Tang S, Huang G, Fan W, Chen Y, Ward JM, Xu X, Xu Q, Kang A, McBurney MW, Fargo DC, Hu G, Baumgart-Vogt E, Zhao Y, Li X. SIRT1-mediated deacetylation of CRABPII regulates cellular retinoic acid signaling and modulates embryonic stem cell differentiation. *Mol. Cell,* **55:** 843-855, 2014.

Retinoid homeostasis is critical for normal embryonic development. Both the deficiency and excess of these compounds are associated with congenital malformations. Here we demonstrate that SIRT1, the most conserved mammalian NAD+-dependent protein

deacetylase, contributes to homeostatic retinoic acid (RA) signaling and modulates mouse embryonic stem cell (mESC) differentiation in part through deacetylation of cellular retinoic acid binding protein II (CRABPII). We show that RA-mediated acetylation of CRABPII at K102 is essential for its nuclear accumulation and subsequent activation of RA signaling. SIRT1 interacts with and deacetylates CRABPII, regulating its subcellular localization. Consequently, SIRT1 deficiency induces hyperacetylation and nuclear accumulation of CRABPII, enhancing RA signaling and accelerating mESC differentiation in response to RA. Consistently, SIRT1 deficiency is associated with elevated RA signaling and development defects in mice. Our findings reveal a molecular mechanism that regulates RA signaling and highlight the importance of SIRT1 in regulation of ESC pluripotency and embryogenesis.

Markunas CA, Xu Z, Harlid S, Wade PA, Lie RT, Taylor JA, Wilcox AJ. Identification of DNA methylation changes in newborns related to maternal smoking during pregnancy. *Environ. Health Perspect.*, **122:** 1147-1153, 2014.

BACKGROUND: Maternal smoking during pregnancy is associated with significant infant morbidity and mortality, and may influence later disease risk. One mechanism by which smoking (and other environmental factors) might have long-lasting effects is through epigenetic modifications such as DNA methylation.
OBJECTIVES: To conduct an epigenome-wide association study (EWAS) investigating alterations in DNA methylation in infants exposed in utero to maternal tobacco smoke, using the Norway Facial Clefts Study.
METHODS: The Illumina HumanMethylation450 BeadChip was used to assess DNA methylation in whole blood from 889 infants shortly after delivery. Out of 889 mothers, 287 reported smoking - twice as many smokers as in any previous EWAS of maternal smoking. CpG sites related to maternal smoking during the first trimester were identified using robust linear regression.
RESULTS: We identified 185 CpGs with altered methylation in infants of smokers at genome-wide significance (q-value < 0.05; Mean $\Delta\beta$= +/- 2%). These correspond to 110 gene regions, of which 7 have been previously reported and 10 are newly confirmed using publically-available results. Among these 10 the most noteworthy are FRMD4A, ATP9A, GALNT2, and MEG3, implicated in processes related to nicotine dependence, smoking cessation, and placental and embryonic development.
CONCLUSIONS: Our study identified 10 genes with newly established links to maternal smoking. Further, we note differences between smoking-related methylation changes in newborns and adults, suggesting possible distinct effects of direct versus indirect tobacco-smoke exposure as well as potential differences due to age. Further work would be needed to determine if these small changes in DNA methylation are biologically or clinically relevant. The methylation changes identified in newborns may mediate the association between in utero maternal smoking exposure and later health outcomes.

Lujan SA, Clausen AR, Clark AB, MacAlpine HK, MacAlpine DM, Malc EP, Mieczkowski PA, Burkholder AB, Fargo DC, Gordenin DA, Kunkel TA. Heterogeneous polymerase fidelity and mismatch repair bias genome variation and composition. *Genome Res.*, **24:** 1751-1764, 2014.

Mutational heterogeneity must be taken into account when reconstructing evolutionary histories, calibrating molecular clocks, and predicting links between genes and disease. Selective pressures and various DNA transactions have been invoked to explain the heterogeneous distribution of genetic variation between species, within populations, and in tissue-specific tumors. To examine relationships between such heterogeneity and variations in leading- and lagging-strand replication fidelity and mismatch repair, we accumulated 40,000 spontaneous mutations in eight diploid yeast strains in the absence of selective pressure. We found that replicase error rates vary by fork direction, coding state, nucleosome proximity, and sequence context. Further, error rates and DNA mismatch repair efficiency both vary by mismatch type, responsible polymerase, replication time, and replication origin proximity. Mutation patterns implicate replication infidelity as one driver of variation in somatic and germ line evolution, suggest mechanisms of mutual modulation of genome stability and composition, and predict future observations in specific cancers.

Pagani JH, Zhao M, Cui Z, Williams Avram SK, Caruana DA, Dudek SM, Young WS. Role of the vasopressin 1b receptor in rodent aggressive behavior and synaptic plasticity in hippocampal area CA2. *Mol. Psychiatry*, epub ahead of print, doi: i: 10.1038/mp.2014.47

The vasopressin 1b receptor (Avpr1b) is critical for social memory and social aggression in rodents, yet little is known about its specific roles in these behaviors. Some clues to Avpr1b function can be gained from its profile of expression in the brain, which is largely limited to the pyramidal neurons of the CA2 region of the hippocampus, and from experiments showing that inactivation of the gene or antagonism of the receptor leads to a reduction in social aggression. Here we show that partial replacement of the Avpr1b through lentiviral delivery into the dorsal CA2 region restored the probability of socially motivated attack behavior in total Avpr1b knockout mice, without altering anxiety-like behaviors. To further explore the role of the Avpr1b in this hippocampal region, we examined the effects of Avpr1b agonists on pyramidal neurons in mouse and rat hippocampal slices. We found that selective Avpr1b agonists induced significant potentiation of excitatory synaptic responses in CA2, but not in CA1 or in slices from Avpr1b knockout mice. In a way that is mechanistically very similar to synaptic potentiation induced by oxytocin, Avpr1b agonist-induced potentiation of CA2 synapses relies on NMDA (N-methyl-D-aspartic acid) receptor activation, calcium and calcium/calmodulin-dependent protein kinase II activity, but not on cAMP-dependent protein kinase activity or presynaptic mechanisms. Our data indicate that the hippocampal CA2 is important for attacking in response to a male intruder and that the Avpr1b, likely through its role in regulating CA2 synaptic plasticity, is a necessary mediator.

AWARDS AND HONORS

Scientific Awards

Dr. Lutz Birnbaumer (Neurobiology Laboratory) was honored with an International Symposium on "Receptors, G Proteins and Integration of Calcium Signaling", organized by the German Center for Cardiovascular Research (DZHK), for his scientific contributions to the topics of the symposium over a span of 45 years. The symposium was held at the Max Delbrueck Communications Center in Berlin-Buch, November 20-22, 2014. Thirty former fellows and colleagues, including NIEHS's Jim Putney and NIDCR's Indu Ambudkar, spoke presenting novel findings and highlighting past breakthroughs in which Dr. Birnbaumer had seminal roles.

Dr. William C. Copeland (Chief, Genome Integrity & Structural Biology Laboratory) received a service award from the United Mitochondrial Disease Foundation for "Outstanding service and commitment to the UMDF Scientific and Medical Advisory Board."

Dr. Saki Gotoh (Reproductive & Developmental Biology Laboratory) received a fellowship from the Japanese Society for the Promotion of Science.

Dr. Ashutosh Kumar (Immunity, Inflammation & Disease Laboratory) received the 2014 Young Investigator Award from the Society of Free Radical Biology and Medicine.

Dr. Thomas A. Kunkel (Genome Integrity & Structural Biology Laboratory) was elected into the American Academy of Arts & Sciences.

Dr. Walter J. Rogan (Epidemiology Branch) received the Zena Stein/Mervyn Susser Lifetime Achievement Award from the Coalition for Excellence in Maternal and Child Health Epidemiology.

Dr. Dale P. Sandler (Chief, Epidemiology Branch) received the Nathan Davis Award for Outstanding Government Service.

Dr. Thomas Van'T Erve (Immunity, Inflammation & Disease Laboratory) received the 2014 Young Investigator Award from the Society of Free Radical Biology and Medicine.

Dr. Samuel H. Wilson (Genome Integrity & Structural Biology Laboratory) received the 2014 Outstanding Science Awards from SER-CAT (Southeast Regional Collaborative Access Team) and presented a talk at the symposium.

Dr. Darryl C. Zeldin (Scientific Director and Immunity, Inflammation & Disease Laboratory) received the National Institute of Child Health and Human Development Partnership Award.

Named Professorships/Lectures

Dr. Karen Adelman (Epigenetics & Stem Cell Biology Laboratory) presented the Keynote Lecture at the June 2014, FASEB summer conference on Prokaryotic Transcription Mechanisms, Saxtons River VT.

Dr. Patricia Jensen (Neurobiology Laboratory) presented the keynote address at the Second Neural Circuit Colloquium in Montpelier, France, June 2014.

Dr. Thomas A. Kunkel (Genome Integrity & Structural Biology Laboratory) delivered the Plenary Lecture at the Duke University Symposium to honor Barbara Shaw; he delivered the Plenary Lecture at the Conference on "DNA Polymerases: Biology, Diseases and

Biomedical Applications", Cambridge, UK; and presented the Keynote Lecture at the Fifth International Symposium on DNA Damage Response & Human Diseases, Beijing, China.

Dr. Stephanie J. London (Epidemiology Branch) was the Charles and Edith McGill Visiting Professor in Occupational and Environmental Medicine at Vanderbilt Medical School, Nashville, TN; presented the James Whittenberger Lecture at Harvard School of Public Health, Boston, MA; and will present the Feldman Lecture at the American Epidemiological Society.

Dr. Dale P. Sandler (Chief, Epidemiology Branch) presented "The Sister Study: Environmental and genetic factors associated with breast cancer and other outcomes in a risk-enriched cohort" as part of the Herbert Irving Comprehensive Cancer Center Distinguished Seminar Series, Columbia University, New York, NY, Feb 2014.

Dr. Carmen Williams (Reproductive and Developmental Biology Laboratory) gave the Roy Hertz Memorial Lecture, "Epigenetic Reprogramming of Female Reproductive Tract Function by Neonatal Estrogen Exposure," at the C. Everett Koop Memorial NIH Symposium on Women's Health Research: A Celebration of Patient-Centered Basic Research, National Institutes of Health Clinical Center, Bethesda, MD.

Dr. Samuel H. Wilson (Genome Integrity & Structural Biology Laboratory) was the Keynote Speaker at the Symposium at the 2014 ASBMB Annual Meeting in San Diego; was the Keynote speaker at the 2014 US-Japan DNA Repair Meeting in Naruto, Japan; chaired the Symposium at the 2014 US-EU DNA Repair Meeting in Santa Fe; and was a Distinguished Guest Speaker at Tulane University in New Orleans.

Dr. Darryl C. Zeldin (Scientific Director and Immunity, Inflammation & Disease Laboratory) was the Keynote Speaker at 2014 Wuhan Symposium on Polyunsaturated Fatty Acids and Metabolism: "Cytochrome P450 Eicosanoids and Cardiovascular Disease;" and was the Keynote Speaker at Nanjing Medical University, School of Public Health, Nanjing, China: "A Vision for Environmental Health: Overview of the NIEHS."

Advisory/Editorial Boards

Dr. Karen Adelman (Epigenetics & Stem Cell Biology Laboratory) served on the Editorial Boards of the journals *Molecular Cell, eLife* and *Genes and Development*. Dr. Adelman was also appointed as a permanent member of the NIH Molecular Genetics A study section.

Dr. Dmitry A. Gordenin (Genome Integrity & Structural Biology Laboratory) served on Board Editor of *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*.

Dr. David S. Miller (Signal Transduction Laboratory) is an Associate Editor of *Journal of Pharmacology and Experimental Therapeutics* and serves on the Editorial Boards of the journals *Toxicology and Applied Pharmacology* and *Journal of Experimental Zoology*.

Dr. Fredrick W. Miller (Clinical Research Branch) is an Associate Editor of the *Journal of Neuromuscular Diseases*.

Dr. Roel Schaaper (Genome Integrity & Structural Biology Laboratory) served on Board Editor of *Mutation Research*.

MENTORING

NIEHS Trainee Alumni

DIR has recently analyzed where recent postdoctoral trainees have gone upon completing their training, what they are doing and the level of the positions they took. Below is a summary of the analysis of 41 postdoctoral trainees that left NIEHS from January 1, 2014 through December 31, 2014.

Where did they go?

Academic institution	17
Government agency	4
For-profit company	12
Non-profit organization	0
Private medical practice	0
Independent/self-employed	1
Unknown or Undecided	7
TOTAL	41

What is the level of their position?

Tenure track faculty	9
Non-tenure track faculty	1
Professional Staff	18
Support staff	0
Management	0
Trainee	6
Unknown or Undecided	7
TOTAL	41

What are they doing?

Additional postdoctoral training	5
Internship	0
Additional advanced degree [1 PA]	1
Primarily teaching	3
Primarily basic research	10
Primarily clinical research	0
Primarily clinical practice	0
Primarily applied research	10
Primarily patient care	0
Regulatory affairs	1
Science administration/project management	2
Intellectual property/ licensing and patenting	0
Consulting	0
Public policy	0
Science writing or communications	2
Grants management	0
Business development or Operations	0
Computation/informatics	0
Sales/marketing	0
Unknown or Undecided	7
TOTAL	41